Remarks

The amendments

Please enter the amendments which raise no new issues for consideration. The amendments merely restrict the scope of the independent claims to the scope of previously existing dependent claims 2-3 and 19-20.

Dependent claims 7-12, 14-15, and 21-24 have also been amended to perfect the antecedent basis. All references to the "anti-tumor agent" have been amended to recite "microtubule stabilizing anti-tumor agent," as recited in the independent claims.

The amendments should be entered because they put the claims in better form for appeal and allowance. Entry of the amendments will reduce issues for appeal.

The rejection of claims 1, 4-18, 21-25, and 27 under 35 U.S.C. § 112, first paragraph

Claims 1, 4-18, 21-25, and 27 stand rejected as failing to enable the full scope of the claimed invention, as is required under § 112. The claims have been amended to recite bacteria selected from the group consisting of *Clostridium novyi* and *Clostridium sordellii,* which the office action notes are two species for which the art and disclosure support the ability to express the required phenotype in order to practice and carry out the claimed invention.

It is respectfully submitted that the claims now correspond in scope to the enablement provided by the specification's teachings, as acknowledged by the U.S. Patent and Trademark Office. Please withdraw the rejection.

The rejection of claims 1-28 under 35 U.S.C. § 103(a)

Claims 1-28 stand rejected as unpatentable over Dang (U.S. 7,344,710) in view of Fojo (*Current Opinions in Oncologic, Endocrine, and Metabolic Investigational Drugs,* 2001, *2:* 293-304), Helson (U.S. 5,688,517), and Dewhirst (US 5,554,638).

All claims recite the combination of spores of a toxin-defective anaerobic bacterium selected from the group consisting of *Clostridium novyi* and *Clostridium sordellii* and a

microtubule stabilizing anti-tumor agent. Claims 13, 15, and 18 additionally recite an inhibitor of NOS.

Dang is cited as teaching the use of spores of a toxin-defective, anaerobic bacterium for treating tumors. Fojo and Helson are cited as teaching microtubule stabilizing agents as anti-tumor agents. Dewhirst is cited as teaching NOS inhibitors for treating tumors. The rejection reasons that because the art taught treating tumors with each of these agents, combining them would have been *prima facie* obvious. More specifically, the rejection urges that it would have been obvious to substitute the Fojo and Helson microtubule stabilizing agents in Dang's combination of spores of a toxin-defective, anaerobic bacterium with microtubule-*de*stabilizing agents, because they were all known to have anti-tumor effects individually.

The U.S. Patent and Trademark Office Examination Guidelines Update published in the Federal Register, vol. 75, no. 169, page 53643-60, September 1, 2010, deals with the effect of *KSR v. Teleflex* on prior obviousness law. The Guidelines Update concludes that "familiar lines of argument still apply, including teaching away from the claimed invention by the prior art, lack of a reasonable expectation of success, and unexpected results."

Reviewing post-*KSR* decisions, the Guidelines Update teaches that "[a] claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results." Page 53647. Moreover, it teaches that "[i]f results would not have been predictable, Office personnel should not enter an obviousness rejection using the combination of prior art elements rationale, and should withdraw such a rejection if it has been made." *Ibid.*

The specification provides a number of unexpected results which have not been considered in making the rejection. First, the specification teaches the unexpected potency of the combination of spores and microtubule stabilizing agents. The agents alone led to a *transient* tumor regression, but the addition of spores led to *cures*. Specification at page 25, lines 5-7. Striking improvements in long term cures are shown in the Kaplan-Meier curves of Figures 6B and 6D and 7B and 7D of the subject application. The inventors' results were reviewed and commented upon by Van Mellaert et al., who stated that the combination of spores with the microtubule stabilizing agents "did not result in haemorrhagic necrosis but in slow regression of the tumour. The addition of *C. novyi-NT* improved the duration of tumour remission in comparison with that obtained with the agents alone, even leading to the cure of mice bearing

specific tumour xenografts." *Trends in Microbiology 14*: 190, 2006 at 191, column 2, lines 26-29. (Exhibit A).

Second, unexpectedly, the combination of microtubule stabilizing agents and spores as claimed in the subject application is less toxic than the prior art combination of microtubule destabilizing agents and spores. "No deaths occurred after treatment with the microtubule stabilizers plus C. novyi-NT, while 4% to 8% of mice treated with microtubule destabilizers plus C. novyi-NT died." Specification at page 22, lines 11-13. See also Table 2, comparing microtubule destabilizers (vinorelbine and HTI-286) and microtubule stabilizers (docataxel and MAC-321). Toxicity was a problem that rankled Dang:

> Treatment of mice with large tumors was sometimes toxic. Approximately 20% of mice with 350 mm^3 tumors and 50% of mice with 700 mm^3 tumors died within 24-72 hours of administration of spores plus D10. No deaths were observed after treatment with C. novyi-NT spores alone or with D10 alone. Though the basis for this toxicity is not yet known, it could have been due to efflux of toxic bacterial products from the tumors or due to "tumor lysis syndrome." It has previously been noted that the rapid lysis of very large tumor burdens is associated with systemic toxicity in humans treated with chemotherapy, perhaps due to the sudden efflux of tumor cell metabolites into the circulation (Altman, 2001). Though tumor lysis syndrome can be controlled in humans, it is difficult to control in mice. Any therapy which dramatically shrinks tumors may be subject to this side effect. Treatments for tumor lysis syndrome which may be used in humans include allopurinol, urate o[x]idase, and volume repletion (hydration). Treatments to mitigate side-effects of anti-tumor agents such as bone marrow toxicity and neutropenia may also be desirable. Such treatment[s] are w[e]ll known in the art and can be employed here in the known manner.

Column 5, lines 16-38. The elimination of this problem using the claimed methods was not *a priori* predictable.

These improvements and synergies in duration of response and reduced toxicity were not expected or predictable and rebut the *prima facie* case of obviousness.

In the prior response, applicants urged that the prior art taught away from the claimed invention.[1] The U.S. Patent and Trademark Office rejected this argument, stating that Dang would only constitute a teaching away "if there was insufficient evidence that microtubule stabilizing agents can treat tumors." The office action explained:

[1] Dang taught the combination of spores with microtubule destabilizing agents.

> However, the secondary prior art clearly teach that these agents also have anti-tumor activity and properties, therefore the selection of well known ingredients which are functional equivalents is *prima facie* obvious. These agents do not have an opposite effect for treating tumors which is what the claims are directed to in the instant case.

This explanation misconstrues when an applicant may argue that the references contain a teaching away. A "teaching away" is a valid argument to rebut a *prima facie* case. M.P.E.P. §2145; see especially subpart X.D. That is, assuming that there is a proper *prima facie* case, evidence can be brought to bear that would lead away from the combination, even though there was an initial reason to think that they could be combined. The reasoning of the office action obviates that procedural opportunity which the law gives to applicants. If the recited agents were known in the art to have an opposite effect, *e.g.,* they were known to enhance tumor growth, that would be an argument against the propriety of the *prima facie* case itself. But that is not all that the law and the guidelines permit under the rubric of "teaching away." The law permits an applicant to provide a reason why, even if there were a proper *prima facie* case, why the ultimate conclusion should be that the invention is not obvious. Applicants have not been given this opportunity, because the office action has permitted the *prima facie* case itself be a reason to exclude the evidence of teaching away. The reason that the U.S. Patent and Trademark Office provided for combining prior art elements including the microtubule stabilizing antitumor agents was because they were known in the art to have an antitumor effect. If that antitumor effect is enough to exclude rebuttal evidence, then the *prima facie* case becomes unassailable, contrary to the guidelines and the law. The M.P.E.P. cautions: "Consideration of rebuttal evidence and arguments requires Office personnel to weigh the proffered evidence and arguments. Office personnel should avoid giving evidence no weight, except in rare circumstances." *In re Grose,* 592 F.2d 1161, 1168, 201 USPQ 57, 63-64 (CCPA 1979.) See also *In re Alton*, 76 F.3d 1168, 1174-75, 37 USPQ2d 1578, 1582-83 (Fed. Cir. 1996).

Applicants request that the U.S. Patent and Trademark Office consider the evidence provided in the cited Dang reference that a beneficial combination of drug with spores would be one that collapses or *de*stabilizes microtubules. See column 4, lines 38-40 and 59-63. Dang not only teaches the use of such drugs, but provides a rationale for using such drugs. "The latter class of agents [that appear to partially collapse tumor vasculature, such as flavone acetic acid derivatives and microtubule binding agents] has been shown to be able to interfere with proper

circulation through the tumors and thereby trap large molecules, such as antibodies or bacteria, that have gained access to the tumor tissue (Theys, 2001)(Pedley, 1999)(Pedley, 2001)." Dang at column 9, lines 1-5. Dang further explained: "Presumably, the vascular collapse further lowered the oxygen tension near the trapped bacteria and thereby increased the potential for bacterial growth." Column 10, lines 25-28. Thus Dang teaches that one should use microtubule *de*stabilizing agents in combination with the bacterial spores in order to trap the bacteria in the tumors. This is an implicit teaching away from combining spores with agents that would have the diametrically opposite effect.

In view of the "teaching away" and of the unexpected results, any *prima facie* case of obviousness that has been made has been rebutted. Such rebuttal follows the U.S. Patent and Trademark Office's own guidelines. Withdrawal of the rejection for obviousness would therefore be proper.

Double Patenting

Claims 1-15 are rejected as nonstatutorily obvious over claims 1-5 and 20 of Dang, U.S. 7344710, in view of Fojo, Helson, and Dewhirst, similar to the prior rejection under § 103. For the same reasons cited in the reply to the prior rejection under § 103, the double patenting rejection should be withdrawn.

The entire teachings of Dang were available in the prior art. The entire teachings of Dang should be considered for their teaching away effect on the double patenting rejection. The unexpected results in the specification of the subject application should also be considered. The unexpected results and the teaching away are sufficient to rebut the nonstatutory rejection for obviousness.

Withdrawal of this rejection is respectfully requested.

Conclusion

A speedy allowance of all claims is requested, as the prior art neither taught nor suggested the combinations as claimed, either as a method of treating or as a kit for treating tumors.

Respectfully submitted,

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